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Abstract: BACKGROUND: Dependent cocaine users consistently display increased trait impulsivity on self-report questionnaires and less consistently exhibit elevated motor impulsivity in some behavioral tasks. However, trait and behavioral impulsivity measures have rarely been investigated in recreational users. Therefore, we examined self-reported trait and motor impulsivities in recreational and dependent cocaine users to clarify the role of impulse control in cocaine addiction and non-dependent cocaine use. METHODS: We investigated relatively pure recreational (n=68) and dependent (n=30) cocaine users, as well as psychostimulant-naïve controls (n=68), with self-report questionnaires (Barratt Impulsiveness Scale 11; Temperament and Character Inventory) and behavioral tasks (Rapid Visual Information Processing Task; Stop-Signal Task). RESULTS: Compared with controls, recreational and dependent cocaine users displayed higher trait impulsivity and novelty seeking scores on self-report questionnaires. Trait impulsivity scores were strongly associated with an increased number of symptoms of depression and attention deficit hyperactivity disorder and correlated significantly with long-term cocaine intake parameters. By contrast, none of the behavioral motor impulsivity measures showed significant group effects or correlated with cocaine use parameters. The correlations among the self-report measures were high, but self-reports were scarcely correlated with behavioral task measures. CONCLUSIONS: These findings suggest that relatively pure cocaine users already display increased trait impulsivity at a recreational level of use. However, the results do not indicate any cocaine-related elevation of behavioral impulsivity in terms of motor or response inhibition. In summary, our data imply that elevated trait impulsivity is not a specific feature of dependent cocaine use.

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Differences in self-reported and behavioral measures of impulsivity in recreational and dependent cocaine users

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Abstract

Background: Dependent cocaine users consistently display increased trait impulsivity on self-report questionnaires and less consistently exhibit elevated motor impulsivity in some behavioral tasks. However, trait and behavioral impulsivity measures have rarely been investigated in recreational users. Therefore, we examined self-reported trait and motor impulsivities in recreational and dependent cocaine users to clarify the role of impulse control in cocaine addiction and non-dependent cocaine use.

Methods: We investigated relatively pure recreational (n=68) and dependent (n=30) cocaine users, as well as psychostimulant-naïve controls (n=68), with self-report questionnaires (Barratt Impulsiveness Scale 11; Temperament and Character Inventory) and behavioral tasks (Rapid Visual Information Processing Task; Stop-Signal Task).

Results: Compared with controls, recreational and dependent cocaine users displayed higher trait impulsivity and novelty seeking scores on self-report questionnaires. Trait impulsivity scores were strongly associated with an increased number of symptoms of depression and attention deficit hyperactivity disorder and correlated significantly with long-term cocaine intake parameters. By contrast, none of the behavioral motor impulsivity measures showed significant group effects or correlated with cocaine use parameters. The correlations among the self-report measures were high, but self-reports were scarcely correlated with behavioral task measures.

Conclusions: These findings suggest that relatively pure cocaine users already display increased trait impulsivity at a recreational level of use. However, the results do not indicate any cocaine-related elevation of behavioral impulsivity in terms of motor or response inhibition. In summary, our data imply that elevated trait impulsivity is not a specific feature of dependent cocaine use.

Keywords: Impulsivity, Cocaine, Recreational use, Stimulants, Addiction, ADHD

1. Introduction

According to the United Nations Office on Drugs and Crime (2012), the annual number of cocaine users (CU) is estimated to be up to 20 million people worldwide. Despite the high addictive potential of cocaine (Nutt et al., 2007), a substantial proportion of CU display a recreational and non-dependent pattern of use (European Monitoring Centre for Drugs and Drug Addiction, 2012).

For years, impulsivity has been recognized as a fundamental feature of substance users (de Wit, 2009). During the past two decades, a growing body of literature has consistently linked impulsivity to the use of cocaine and postulated impaired cognitive control in CU (Beveridge et al., 2008; Bolla et al., 2004; Garavan and Hester, 2007). This relationship has recently been investigated with not only behavioral techniques but also neurobiological and imaging techniques (Perry and Carroll, 2008). Because such imaging studies in chronic CU have repeatedly reported reductions in gray matter density in the dorsolateral prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex (Bolla et al., 2004; Ersche et al., 2011; Franklin et al., 2002; Matochik et al., 2003), evidence has accumulated that cocaine affects the very same brain regions that are crucially involved in cognitive control (Beveridge et al., 2008; Cabeza and Nyberg, 2000; Garavan and Hester, 2007) and, consequently, impulsivity (Dalley et al., 2011; Garavan and Hester, 2007).

Impulsivity, a construct with multiple facets (Evenden, 1999), is generally defined as behavior that occurs rapidly and lacks planning and foresight (Moeller et al., 2001a). Various instruments exist that measure a range of attitudes generally termed as “impulsive” (Dawe et al., 2004). Regarding substance use, previous studies primarily focused on constructs such as trait impulsivity, disinhibition, novelty seeking, and reward discounting (Dawe et al., 2004; de Wit, 2009). Whereas trait impulsivity was mainly assessed with self-report questionnaires relying on individual self-perception, impulsive action or choice was assessed with behavioral tasks (Winstanley et al., 2010). However, trait and behavioral impulsivity measures commonly displayed only slight correlations in healthy individuals (Lijffijt et al., 2004; Reynolds et al., 2006).

Chronic or dependent cocaine use has consistently been associated with higher scores for trait impulsivity and novelty seeking on self-report questionnaires. Research has also revealed that dependent cocaine users (DCU) display impaired performance in behavioral impulsivity measures

such as Stop-Signal and Go/No-go tasks (Ersche et al., 2010; Perry and Carroll, 2008; Verdejo-Garcia et al., 2008). Preliminary data from a small study using the Stop-Signal Task (SST) have also suggested impaired inhibitory control in recreational cocaine users (RCU)(Colzato et al., 2007). Additionally, a large study has confirmed higher self-reported impulsivity in recreational stimulant users (Reske et al., 2010).

Although the link between impulsivity and cocaine use seems to be proven, there exists a lack of clarification on the relation between different facets of impulsivity and the extent of cocaine use. It is also unknown whether elevated impulsivity affects only DCU or whether RCU are also affected. Clarifying this issue is important notably in regard to risk markers, prevention, and treatment success (Patkar et al., 2004). Studies investigating impulsivity in a large sample of pure RCU, with little or no polydrug use, do not exist. Furthermore, impulsivity analysis studies categorized for groups of differing cocaine use patterns, ranging from RCU to DCU, have not been published thus far. Therefore, we investigated fairly large samples of relatively pure RCU, DCU, and matched stimulant-naïve healthy controls with a comprehensive battery of commonly used impulsivity measures (de Wit, 2009; Perry and Carroll, 2008). The aims were to examine different aspects of impulsivity and to clarify the role of impulsivity in cocaine addiction and controlled use. Based on previous results of elevated impulsivity scores in DCU, we expect to find increased trait and behavioral impulsivity in DCU and similar, albeit less pronounced, results in RCU. Because attention deficit hyperactivity disorder (ADHD)(Wilson, 2007), craving (Tziortzis et al., 2011), and depression (Swendsen and Merikangas, 2000) have been linked to both impulsivity and substance use, we also assessed their relationships with cocaine use. Finally, by performing quantitative urine and hair toxicology analyses, we were able to characterize objectively the participants' drug use over the past six months.

2. Methods

2.1 Participants

The study included 68 RCU, 30 DCU, and 68 healthy and cocaine-naïve controls (recruitment and selection details Supplementary Methods 1[1]). Specific inclusion criteria for the two user groups were cocaine as the primary used illegal drug, cocaine use of >0.5g per month, and abstinence duration of <6 months. Cocaine dependence was diagnosed in accordance with the *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV)(American Psychiatric Association, 1994), with only DCU fulfilling the dependence criteria. Exclusion criteria for all participants were an acute or previous neurological disorder or head injury, any clinically significant medical diseases, and use of prescription drugs affecting the brain. Additional exclusion criteria for the control subjects were any Axis I DSM-IV psychiatric disorder, including ADHD, and any form of addiction or regular illegal drug use (lifetime >15 occasions), with the exception of recreational cannabis use. Specific exclusion criteria for the CU groups were use of opioids, a polytoxic drug use pattern, and any Axis I DSM-IV adult psychiatric disorders – with the exception of cocaine, cannabis, and alcohol abuse; history of affective disorders (acute major depression was excluded); and ADHD. All participants were asked to abstain from illegal substances for a minimum of 72h and from alcohol for at least 24 h before the testing session. Compliance with these instructions was controlled by urine and 6-month hair toxicologies (Supplementary Methods 2). The study was approved by the Cantonal Ethics Committee of Zurich. All participants provided written informed consent and were compensated for their participation.

2.2 Procedure

The cross-sectional data presented in this article were collected as part of the longitudinal Zurich Cocaine Cognition Study ($ZuCo^2St$) (Hulka et al., submitted; Preller et al., 2013; Vonmoos et al., 2013). The Structured Clinical Interview for DSM-IV Axis I (SCID-I) disorders was carried out by

[1] Supplementary material is available by accessing the online version of this paper. Please see Appendix A for more information.

trained psychologists. The Mehrfachwahl Wortschatz Intelligenztest (MWT-B) was applied to estimate premorbid verbal intelligence (Lehrl, 1999). Drug use was assessed by means of a structured and standardized Interview for Psychotropic Drug Consumption (Quednow et al., 2004). The brief version of the Cocaine Craving Questionnaire (CCQ) was used to capture current cocaine craving (Sussner et al., 2006). The current severity of depression was measured by the Beck Depression Inventory (BDI)(Beck et al., 1961), and the ADHD self-rating scale (ADHD-SR)(Roesler et al., 2004) captured the DSM-IV criteria of ADHD. To consider the various aspects of impulsivity, we applied four measures often used in substance use studies (de Wit, 2009; Perry and Carroll, 2008): two self-report questionnaires for trait impulsivity (*Barratt Impulsiveness Scale, BIS-11*) (Patton et al., 1995) and novelty seeking (*Temperament and Character Inventory Novelty Seeking Scale, TCI NS*) (Cloninger et al., 1999) as well as the two behavioral tasks, *Rapid Visual Processing* (*RVP*; www.cantab.com) and *SST* (Logan, 1994) for motor or response inhibition (details in Supplementary Methods 3). The RVP was based on a standardized procedure described in the test manual (www.cantab.com), and the SST was based on the stop-signal paradigm software STOP-IT (Verbruggen et al., 2008). The SST requires subjects to respond quickly to pseudo-randomly presented visual go-signals on a computer screen (arrows to left/right, 50% each) and to inhibit a response when an auditory stop-signal occurs (25% of trials). Thirty-two not further analyzed practice trials were followed by three blocks of 64 trials. A staircase tracking procedure systematically varied the time between the go stimuli and stop signals until the stop-signal delay was found (the point when the participant was able to inhibit the responses 50% of the time).

The behavioral tasks were always presented in the same order during a standard neuropsychological test battery, as published elsewhere (Vonmoos et al., 2013). Participants were allowed to take breaks at any time, and smoking was permitted during the breaks.

2.3 Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 19.0. Frequency data were analyzed by means of Pearson's chi-square test, and quantitative data by analysis of variance (ANOVA). Sidak post-hoc comparisons were performed based on significant main effects.

Because evidence suggests that some facets of impulsivity change throughout the life span (Steinberg et al., 2008), age was introduced as a covariate in analysis of covariance (ANCOVA; uncorrected ANOVA in Supplementary Table 1). Pearson's product-moment correlation analyses were conducted across a consolidated CU group to relate cocaine use parameters to each other and to impulsivity measures. Cumulative cocaine use and weekly use in grams were ln-transformed for statistical analyses because of the highly skewed distribution and the resulting deviation from the normal distribution (Shapiro-Wilk $W<.001$).

Some data were missing owing to incomplete questionnaires (TCI: 1 control, 2 DCU) or technical failures (RVP: 1 control; SST: 1 control, 1 RCU, 1 DCU; urine toxicology: 1 RCU; hair toxicology: 3 controls, 1 RCU).

For the SST parameter stop-signal reaction time (SSRT), reliable estimates, as calculated in this study, depend on a horse-race model with a staircase tracking procedure, resulting in a probability (respond/signal) of ideally .5 (Verbruggen et al., 2008). Because the SSRT analysis is not useful for subjects significantly differing from this value (Verbruggen et al., 2008), we excluded an additional 6 participants (2 controls, 2 RCU, 2 DCU) with a deviation of more than two standard deviations of the total sample.

Possible confounding factors (recent cocaine/cannabis use, age of onset, duration of cocaine use, cocaine binging, craving for cocaine, ADHD, and depression) were defined based on theoretical a priori considerations (Supplementary Methods 4). To limit the data volume, we focused on the most common parameters of the four measures.

3. Results

3.1 Demographic characteristics and drug use

The groups were matched for age, sex distribution, smoking status, and verbal IQ (Table 1). However, DCU had fewer years of education than controls and RCU. As expected, all three groups differed significantly in BDI and ADHD-SR scores, with DCU scoring highest and controls scoring lowest. Hair samples revealed a clear dominance of cocaine compared with other illegal drugs, as set out by the inclusion criteria (Table 2). Notably, hair concentrations of cocaine and its metabolites were highly correlated with self-reported cumulative dose and duration of use (Supplementary Table 2). Although the RCU were regular CU, with a mean weekly consumption of about 1g of cocaine, they did not fulfill the DSM-IV criteria for dependence. Some participants tested positive for cocaine and cannabis in urine screening; instead of excluding these participants, we decided to investigate the acute and post-acute effects of the drugs on these participants.

3.2 Impulsivity measures

BIS-11. RCU and, to an even greater extent, DCU exhibited elevated trait impulsivity, as measured by the BIS-11 total score (linear trend: $p_{trend}<.001$) (Table 3, Figure 1), compared with controls. Similarly, all three subscales showed significant main group effects ($p_{trend}<.01$). In particular, attentional impulsiveness differed significantly among all three groups, whereas motor and non-planning impulsiveness showed substantial increments in both user groups but did not differentiate between them. Correlation analyses within the consolidated group of CU indicated an association between all BIS-11 scales and the two long-term cocaine use parameters of cumulative dose and duration of cocaine use (Table 4), as well as the number of ADHD and depression symptoms (Table 5). Furthermore, attentional impulsiveness correlated strongly with craving for cocaine (Table 4).

TCI NS. Both CU groups showed substantially higher scores than controls in the NS total score, as well as in the sub-scores for extravagance, disorderliness, and, to a lesser degree, impulsiveness. RCU did not significantly differ from DCU for any of these scores (Table 3, Figure 1). The exploratory

excitability scores were quite similar for all three groups, but they negatively correlated with the cocaine metabolites, benzoylecgonine and norcocaine, in the hair samples (Table 4).

RVP. The response bias B" and a calculated impulsivity-score (=$z_{\text{false alarms}} - z_{\text{latency}}$, Supplementary Methods 3) revealed gradual group differences, but neither a main group effect nor significant linear trends (B": p_{trend}=.15; impulsivity-score: p_{trend}=.16) occurred (Table 3, Figure 1). Similarly, no substantial effects were found for mean latency. Total false alarms featured a linear trend (p_{trend}< .05) and a substantial main group effect, but they were missing significant Sidak comparisons. None of these indicators showed a significant correlation with cocaine use parameters (Table 4).

SST. None of the SST parameters revealed a significant main group effect. For the main parameter SSRT, the results did not change (Table 3, Figure 1, Supplementary Figure 1) when we again included the 6 participants (2 controls, 2 RCU, 2 DCU) with more than two standard deviations of the total sample (F(2,159)=2.07, p=.13); when we excluded all participants (8,10,2) with an SST software-based exclusion criterion of p=.0, which determined all subjects with an inhibition rate of significantly more or less than 50% (Verbruggen et al., 2008) (F(2,133)=1.08, p=.34); or when we focused only on CU with negative (65,55,16; F(2,132)=1.73, p=.18) or positive (65,10,11; F(2,82)=1.17, p=.32) urine samples for cocaine. Furthermore, none of these SST parameters did substantially correlate with a cocaine use parameter (Table 4).

3.3 Correlation analysis

The two self-report measures of BIS-11 und TCI NS were – with the exception of the TCI subscale, exploratory excitability – all positively correlated (Table 5). By contrast, none of the correlations between the two behavioral tasks was significant. Of the 81 correlations between self-report and behavioral impulsivity measures, only 2 correlations fell below a significance level of p<.01 (BIS-11 non-planning impulsiveness and SST p(correct inhibition); TCI disorderliness and SST RT on go trials).

3.4 Cofactor analyses

ANCOVAs with controls and CU subgroups stratified for either cocaine or cannabis urine toxicology status (pos/neg), age of onset (>18/≤18 years), duration of cocaine use (≤10/>11 years), binge use (low/high), craving (low/high), ADHD (with/without), or depression (low/≥mild) (group assignments Supplementary Methods 4) revealed significant main group effects in the BIS-11 and TCI NS total scores for all eight cofactors (Supplementary Table 3). These effects are primarily based on substantial differences between controls and both CU subgroups. In-depth analysis of the factor duration of cocaine use suggested that trait impulsivity measured with the BIS-11 was more pronounced in long-term users (>10 years), a link that already became apparent in the significant correlations of the BIS-11 scores with years of cocaine use. Moreover, early age of onset was associated with slightly elevated BIS-11 total scores, again confirming the significant correlation of both parameters (Table 4). In line with recent studies (Crunelle et al., 2012; Ekinci et al., 2011; Nandagopal et al., 2011), the presence of ADHD or mild depression (BDI≥11) was associated with substantially higher BIS-11 total scores. For the two behavioral measures, RVP B" and SSRT, no main group effects were found.

4. Discussion

The aims of the present study were to examine trait and behavioral impulsivities in RCU and DCU and to clarify the role of impulsivity in cocaine addiction in contrast to controlled recreational use. The performance of hair toxicologies and comprehensive psychiatric diagnostics allowed the investigation of relatively pure cocaine users with little psychiatric comorbidity. As expected, CU displayed higher trait impulsivity and novelty seeking on self-report questionnaires (BIS-11, TCI) than controls; however, with the exception of the BIS-11 subscale attentional impulsiveness, RCU did not differ from DCU. Thus, elevated trait impulsivity is not an exclusive feature of addicted CU. Furthermore, more pronounced trait impulsivity was associated with an increased number of ADHD and depression symptoms in CU and with longer duration of cocaine use and higher cumulative dose. By contrast, none of the behavioral motor impulsivity measures (RVP, SST) showed significant group effects or correlated with any cocaine use parameter. Moreover, correlations among the self-report impulsivity measures were high, but none of the intercorrelations between behavioral task parameters was significant. In addition, we found that self-reports correlated only slightly with behavioral measures. This finding confirms those of previous studies with healthy controls (Lijffijt et al., 2004; Reynolds et al., 2006) and substance users (Clark et al., 2006; Ersche et al., 2011) that also reported no or only weak correlations between trait and behavioral impulsivity measures. Therefore, our results support the assumption that impulsivity is a multidimensional construct and that, to date, no comprehensive model exists that integrates all these seemingly important features of impulsivity (Perry and Carroll, 2008).

We found elevated trait impulsivity for RCU and, to an even greater extent, for DCU, thus confirming previous reports of higher BIS-11 scores for DCU compared with healthy controls (Ersche et al., 2011; 2010; Moeller et al., 2002). Similarly, the only recently published report that included RCU described enhanced BIS-11 total scores for 155 recreational prescription stimulant users but featured no separate analysis for the subgroup of 43 RCU (Reske et al., 2010).

Together with the correlations between BIS-11 scores and several cocaine use parameters detected in the present study, these findings indicate a robust relationship between self-reported trait impulsivity

and cocaine use. However, in our cross-sectional design, we cannot determine whether these impulsivity traits were preexistent, drug induced, or both. Our results also revealed ADHD and depression to be important factors with regard to trait impulsivity in CU. These findings are in line with the frequent comorbidity of ADHD and depression with substance use disorders (Swendsen and Merikangas, 2000; van Emmerik-van Oortmerssen et al., 2012), with which they share some fundamental features: Whereas ADHD is characterized by inattentive and impulsive behavior (Wilson, 2007), there is evidence supporting a relationship between trait impulsivity and depression, especially as the BIS-11 total score is related to hopelessness and depression (Swann et al., 2008). Moreover, our results confirm that of a recent small study in which ADHD in CU was associated with strongly increased trait impulsivity, as measured with the BIS-11 (Crunelle et al., 2012). By contrast, we found that craving for cocaine seemed to be only marginally associated with the BIS-11 total score, a finding that is in line with earlier studies (Moeller et al., 2001b; Tziortzis et al., 2011). Unlike in previous studies investigating alcohol binge drinking (Moreno et al., 2012) and binge eating (Waxman, 2009), we found that a cocaine binge profile was not associated with more pronounced trait impulsivity.

Novelty seeking, as measured by the Tridimensional Personality Questionnaire or its successor TCI, has repeatedly been linked to substance use (Lukasiewicz et al., 2008; Prisciandaro et al., 2012; Sher et al., 2000). A study focusing on stimulant-dependent individuals (with 93% DCU) found that these drug users reported higher sensation-seeking behavior than controls (Ersche et al., 2010), which is in line with the present findings indicating enhanced novelty seeking in CU in general but no substantial differences between RCU and DCU. Thus, increased novelty seeking does not seem to be decisive for the amount or pattern of cocaine use. Notably, a recent study found no difference between controls and DCU in the sensation-seeking subscale of the UPPS-P impulsive behavior scale (Albein-Urios et al., 2012). However, this subscale consisted of only 12 items and included two aspects of novelty seeking (tendency for exciting activities and openness for new experiences), whereas the TCI NS scale also tested for impulsiveness. Because we did not find any group differences in our TCI subscale of exploratory excitability, capturing similar aspects as the UPPS-P sensation seeking score (Cloninger et

al., 1999), it might be concluded that impulsive rather than explorative aspects of novelty seeking are associated with repeated cocaine use.

None of the four RVP parameters proposed as impulsivity measures (Ersche et al., 2011) displayed significant group differences between CU groups and the control group. Thus, we replicated a recent study reporting no significant differences between controls and DCU for the RVP parameters B", total false alarms, and mean latency (Ersche et al., 2011). Previous research involving the RVP, which is typically used for measuring sustained attention, has revealed that the standard parameters for sustained attention (A', total hits) showed clear group differences between DCU and controls in both samples (Ersche et al., 2011; Vonmoos et al., 2013). Only a single study has used the RVP to investigate impulsivity in RCU, albeit in a small sample size of 17 RCU and 24 controls (Soar et al., 2012). These authors reported a delayed mean latency in recreational users (p = .03), a finding that also does not support elevated behavioral impulsivity in RCU. However, it should be noted that the total number of false alarms was included in three of four RVP measures, and the false alarm rate was relatively low in all three groups. Consistent with previous findings, we thus confirm that these RVP parameters are not suitable in distinguishing impulsive behavior between controls and CU.

Previous studies in which the SST was applied to CU mostly found that CU showed decreased motor response inhibition, as measured by the main parameter SSRT (Verdejo-Garcia et al., 2008). Given that we found neither group differences nor any association with cocaine use patterns or parameters regarding the SSRT, we were unable to confirm these previous results. A previous study suggested that the abstinent duration in CU might play a role in motor impulsivity tasks (Li et al., 2010). In our study, CU reported a relatively long mean abstinence duration of ~25 days. A study that included DCU with a comparable abstinence period of at least 2 weeks showed slightly increased SSRT in these users (p <.05; d≈.65), but this difference was eliminated by adjustment for the post-signal slowing effect (Li et al., 2006). Other studies that included RCU (Colzato et al., 2007; Fillmore and Rush, 2002) or DCU (Ersche et al., 2011; 2012) found significant group differences between CU and controls in SSRT showing moderate effect sizes. The main difference between these studies and ours

is that CU either had recently used cocaine (Ersche et al., 2011; 2012; Fillmore and Rush, 2002) or reported an abstinence duration of at least 2 days, which was not further verified (Colzato et al., 2007). Because our separate comparisons of CU with positive (n=21) or negative (n=71) urine samples did not show any group differences, we, however, cannot replicate these results either. Regarding the reaction time on go-signal, our data did not show significant group differences, a finding in line with those of previous studies investigating RCU (Colzato et al., 2007; Fillmore and Rush, 2002) or DCU (Li et al., 2006).

In summary, our SST results are largely similar to previous findings. However, with regard to the SSRT, none of our calculations with different sample compositions (ADHD, positive urine toxicology, etc.) could confirm an association with cocaine use. In this sense, we agree with Ersche et al. (2012) that impaired inhibitory control might not result from long-term drug use, but, in contrast to these authors, we also cannot conclude that deficient inhibitory motor control – as measured with the SSRT – is a familial trait of CU.

Given that the SSRT performance can be influenced by many factors, other possible reasons for conflicting results exist:

i) In most previous studies, different SST designs were applied, including different stimuli or signals, interval steps, numbers of blocks and trials, and probabilities of go trials. Accordingly, not all SST designs might have the same sensitivity in detecting group differences. We used an SST design consisting of three blocks of 64 trials, which might be less sensitive than SST designs with five blocks of 64 (Ersche et al., 2012) or 104 trials (Colzato et al., 2007).

ii) The absolute SSRT values in the present study and those of two previous studies using a similar but extended SST design with five blocks of 64 trials are comparable. Our study found that RCU and DCU had SSRT values between 277ms and 293ms, and the DCU in the two previous studies had mean SSRT values of 263ms and 281ms (Ersche et al., 2011; 2012). Whereas our controls revealed a mean SSRT of 298ms, controls from these previous studies displayed much lower SSRTs (235ms/239ms). Therefore, the conflicting results of the present study versus those of (Ersche et al., 2011; 2012) arise from differences between the control groups, not between the CU groups.

iii) Our sample is so far the first to comprise relatively pure CU, as confirmed by hair toxicologies. Therefore, it is possible that previous studies, non of which have applied hair toxicologies, measured the effect of polytoxic drug use, not pure cocaine use. Because subjects addicted to multiple substances have shown higher impulsivity scores on self-report questionnaires than subjects addicted to only one substance (McCown, 1988; O'Boyle and Barratt, 1993), it is reasonable to compare motor impulsivity in pure CU with that of CU with polysubstance use in future research.

iv) Impulsivity is associated not only with substance use disorders but also with several personality disorders, bipolar disorder, and ADHD (Moeller et al., 2001a; Wilson, 2007). Because the co-occurrence of cocaine dependence and personality disorders is associated with enhanced impulsivity (Albein-Urios et al., submitted), we tried to exclude subjects with severe psychiatric disorders or to analyze systematically their interaction with impulsivity. However, differences in the presence of comorbidities related to impulsive behavior between study samples might be another explanation for the conflicting SSRT results.

v) Several methods of estimating SSRT exist (Logan, 1994). One of them, the subtraction method (used in this study), is not suitable for subjects who inhibit significantly more or less than 50% of the trials. This situation can be handled either by excluding these subjects or by calculating the SSRT with another method (Verbruggen et al., 2008). Because the significance level of deviance can be interpreted in multiple ways, as well as the fact that not all studies applying SSRT exclude participants failing to fit the horse-race model or declare the exact estimation method, we cannot rule out that the SSRT calculation itself implies a fundamental data bias in previous studies.

This study has the following limitations: i) Because the DSM-IV criteria for cocaine dependence completely relies on self-perception but ignores the amount or duration of cocaine use, some subjects in the RCU group might be misclassified. ii) We employed hair toxicologies to quantify objectively illegal drug use in the last 3 to 6 months (depending on hair length) but had to rely on self-reports before this period of time. iii) The cross-sectional design of this study makes it impossible to determine the causal relationship between impulsivity and cocaine use.

In conclusion, the present study confirms previous findings of elevated trait impulsivity and novelty seeking scores in CU compared with controls. Given that both recreational cocaine use and dependent cocaine use were associated with higher trait impulsivity, it is not an exclusive feature of addicted cocaine use. Trait impulsivity was strongly associated with an increased number of ADHD and depression symptoms and correlated significantly with long-term cocaine intake parameters. By contrast, none of the behavioral motor impulsivity measures in this study showed significant group effects or correlated with cocaine use parameters. However, it remains unclear if there is a dissociation between trait impulsivity and motor impulsivity or if the differences rather highlight difficulties in the operationalization and measurement of motor impulsivity. Furthermore, in accordance with the current literature, the correlations among the self-report impulsivity measures were high; however, self-reports were scarcely correlated with behavioral impulsivity task measures. Finally, although our results do not indicate any cocaine-related elevation of behavioral impulsivity in terms of motor or response inhibition, other studies have consistently reported increased behavioral impulsivity for DCU in terms of reward discounting (Heil et al., 2006; Hulka et al., submitted).

Figure 1: Comparison of z-standardized impulsivity measures in recreational (RCU) and dependent (DCU) cocaine users as well as controls. Mean z-scores and standard errors (corrected for age). The main parameters of the four measures were z-transformed based on means and standard deviations of the control group. If necessary, test scores were reversed so that higher bars always indicated higher trait impulsivity (BIS-11) / novelty seeking (TCI NS) / motor impulsivity (RVP, SST). Sidak post-hoc tests: *$p<.05$; **$p<.01$; ***$p<.001$.

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Table 1
Demographic data

	Controls	RCU	DCU	$F/\chi^2/T^a$	df, df_{err}	p
N	68 (41%)	68 (41%)	30 (18%)			
Age (y)	30.3 (9.2)	28.7 (6.2)	32.5 (9.0)	2.39[a]	2, 163	.10
Sex (f/m)	21 / 47	18 / 50	8 / 22	0.38[b]	2	.83
Verbal IQ (MWT-B)	104.4 (9.7)	103.2 (9.6)	99.7 (9.1)	2.46[a]	2, 163	.09
School education (y)	10.7 (1.8)	10.5 (2.0)	9.5 (1.2)**°	4.82 [a]	2, 163	**.01**
Smoking / Non-smoking[d]	53 / 15	53 / 15	24 / 6	0.06[b]	2	.97
ADHD-SR sum score (0-22)	7.6 (4.8)	13.2 (9.0)***	17.1 (8.7)***°	19.52 [a]	2, 163	**<.001**
ADHD DSM IV (y/n)[e]	0 / 68	14 / 54	8 / 22	18.27[b]	2	**<.001**
BDI sum score (0-63)	4.6 (4.4)	7.4 (6.1)*	11.8 (8.6)***°°	15.01 [a]	2, 163	**<.001**
BDI depression status (y/n)[f]	5 / 63	17 / 51	12 / 18	15.07[b]	2	**<.001**
Craving for cocaine (0-70)	-	19.0 (9.1)	20.3 (11.4)	0.60[c]	1, 96	.55

Means and standard deviations. Significant p values are shown in bold. Sex, smoking, BDI depression status, and ADHD-SR DSM-IV are shown in frequency data.
[a] ANOVA F-test (all groups), [b] χ^2 test (all groups) for frequency data, or [c] independent T-test (cocaine users only).
[d] Smoking habits were assessed by the Fagerstroem Test of Nicotine Dependence (Heatherton et al., 1991).
[e] ADHD-SR, ADHD self rating scale (cut-off DSM-IV criteria).
[f] BDI, Beck Depression Inventory (cut-off ≥11).
[*] Significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001.
[°] Significant Sidak post-hoc test vs. RCU group: °p<.05; °°p<.01.

Table 2
Pattern and amount of drug use

	Controls (n=68)	RCU (n=68)	DCU (n=30)
Cocaine			
Times per week[a]	-	1.1 (1.0)	2.9 (2.6)
Grams per week[a]	-	1.1 (1.4)	7.9 (15.8)
Years of use	-	6.5 (4.0)	9.4 (6.5)
Maximum dose (grams/day)	-	3.5 (2.5)	9.4 (8.4)
Cumulative dose (grams)	-	519.7 (751.2)	5500.9 (9635.2)
Last consumption (days)[b]	-	27.5 (37.6)	21.0 (33.6)
Hair analysis $Cocaine_{total}$ pg/mg[c,e]	-	3347 (5580)	27798 (40226)
Hair analysis Cocaine pg/mg[c]	-	2739 (4628)	22164 (32609)
Hair analysis Benzoylecgonine pg/mg[c]	-	546 (919)	5048 (7711)
Hair analysis Cocaethylene pg/mg[c]	-	276 (316.)	2006 (3656)
Hair analysis Norcocaine pg/mg[c]	-	62 (101)	586 (758)
Urine toxicology (neg/pos)[d]	68 / 0	57 / 10	18 / 12
Alcohol			
Grams per week[a]	116.8 (122.6)	167.8 (117.5)	188.5 (260.6)
Years of use	13.2 (9.3)	11.2 (5.1)	13.5 (9.5)
Nicotine			
Cigarettes per day[a]	9.3 (9.5)	11.7 (8.8)	15.7 (13.5)
Years of use	9.2 (9.2)	9.6 (6.4)	14.2 (9.3)
Cannabis			
Grams per week[a]	0.5 (1.0)	0.9 (2.1)	1.2 (3.7)
Years of use	4.7 (6.5)	7.7 (6.0)	10.5 (9.9)
Cumulative dose (grams)	358.3 (846.2)	1042.8 (1780.0)	3550.3 (5959.0)
Last consumption (days)[b]	36.2 (50.1); n=33	22.1 (32.3); n=44	25.7 (32.8); n=20
Urine toxicology (neg/pos)[d]	58 / 10	55 / 12	20 / 10
Amphetamine			
Grams per week[a]	0.0 (0.0)	0.1 (0.2)	0.0 (0.2)
Years of use	0.0 (0.1)	1.6 (3.0)	1.5 (3.2)
Cumulative dose (grams)	0.2 (1.4)	21.2 (56.8)	22.3 (62.8)
Last consumption (days)[b]	121.6 (0.0), n=1	61.8 (51.3); n=25	78.4 (75.4); n=6
Hair analysis Amphetamine pg/mg[c]	1 (7)	76 (257)	60 (169)
MDMA			
Tablets per week[a]	-	0.1 (0.3)	0.4 (1.8)
Years of use	0.3 (1.7)	2.5 (3.8)	3.1 (5.2)
Cumulative dose (tablets)	0.9 (2.9)	35.9 (90.5)	157.4 (393.5)
Last consumption (days)[b]	-	75.1 (84.8); n=20	82.1 (45.4); n=9
Hair analysis MDMA pg/mg[c]	3 (16)	545 (1598)	255 (653)
Hallucinogens			
Cumulative dose (times)	0.9 (2.2)	6.0 (14.6)	6.9 (11.8)

Means and standard deviations. Use frequency, duration of use, and cumulative doses are averaged within the total group.
[a] Average use during the last 6 months.
[b] Last consumption is averaged only for persons who used the drug in the last 6 months. In this case, sample size (n) is shown.
[c] Cut-off values for cocaine = 500 pg/mg and for amphetamines/MDMA = 200 pg/mg (Cooper et al., 2012).
[d] Cut-off values for cocaine = 150 ng/ml and for Tetrahydrocannabinol 50 ng/ml (Substance Abuse and Mental Health Services Administration, 2008).
[e] $Cocaine_{total}$ (= Cocaine + Benzoylecgonine + Norcocaine) is a more robust procedure for discrimination between incorporation and contamination of hairs (Hoelzle et al., 2008).

Table 3
Impulsivity measures

Measure	n[a]	Controls	RCU	DCU	F	df, df_{err}	p	p, Sidak post-hoc: Controls vs. RCU	p, Sidak post-hoc: Controls vs. DCU	p, Sidak post-hoc: RCU vs. DCU	Cohen's d: Controls vs. RCU	Cohen's d: Controls vs. DCU	Cohen's d: RCU vs. DCU
Barratt Impulsiveness Scale (BIS-11)													
FI Attentional Impulsiveness	68/68/30	14.7 (0.4)	16.3 (0.4)	18.7 (0.7)	12.982	2, 162	**<.001**	**.03**	**<.001**	**.01**	.42	1.04	.62
FII Motor Impulsiveness	68/68/30	22.5 (0.5)	24.3 (0.6)	25.9 (0.8)	6.435	2, 162	**.002**	.06	**.003**	.33	.39	.73	.33
FIII Nonplanning Impulsivenes	68/68/30	26.3 (0.5)	27.9 (0.5)	29.1 (0.8)	4.570	2, 162	**.01**	.11	**.02**	.56	.35	.61	.26
Bis-11 Total score	68/68/30	63.4 (1.3)	68.5 (1.3)	73.6 (1.9)	10.803	2, 162	**<.001**	**.02**	**<.001**	.08	.46	.93	.47
Temperament and Character Inventory													
NS1 Exploratory excitability	67/68/28	7.5 (0.3)	8.0 (0.3)	7.2 (0.4)	1.904	2, 159	.15	.34	.92	.24	.26	.13	.39
NS2 Impulsiveness	67/68/28	4.8 (0.3)	5.9 (0.3)	6.0 (0.5)	4.258	2, 159	**.02**	**.03**	.09	1.00	.44	.48	.04
NS3 Extravagance	67/68/28	5.8 (0.2)	7.1 (0.2)	7.4 (0.4)	9.486	2, 159	**<.001**	**<.001**	**.002**	.89	.61	.75	.14
NS4 Disorderliness	67/68/28	4.4 (0.2)	5.8 (0.2)	5.7 (0.4)	10.348	2, 159	**<.001**	**<.001**	**.008**	1.00	.68	.64	.04
Novelty seeking Total score	67/68/28	22.5 (0.7)	26.8 (0.7)	26.3 (1.1)	11.384	2, 159	**<.001**	**<.001**	**.009**	.96	.73	.64	.10
Rapid Visual Processing Task													
Response bias B'	67/68/30	.949 (0.0)	.937 (0.0)	.928 (0.0)	1.160	2, 161	.32	.67	.39	.90	.18	.32	.14
Mean latency (ms)	67/68/30	404.7 (11.0)	418.3 (11.0)	416.2 (16.6)	.421	2, 161	.66	.76	.92	1.00	.15	.13	.02
Total false alarms	67/68/30	1.3 (0.2)	1.9 (0.2)	2.1 (0.4)	2.850	2, 161	.06	.19	.11	.89	.32	.46	.14
Impulsivity-score	67/68/30	.00 (0.2)	.23 (0.2)	.44 (0.3)	1.114	2, 161	.33	.70	.40	.88	.17	.31	.15
Stop-Signal Task													
p(correct inhibition)[b]	67/67/29	54.8 (1.4)	54.7 (1.4)	50.4 (2.1)									
RT on go trials (ms)[c]	67/67/29	765.2 (23.2)	728.7 (23.3)	734.4 (35.6)	.671	2, 159	.51	.61	.85	1.00	.19	.16	.03
p(correct responses on go trials)[b]	67/67/29	94.4 (1.4)	90.9 (1.4)	94.0 (2.1)	1.759	2, 159	.18	.21	1.00	.53	.31	.03	.28
RT on signal-respond trials (ms)[c]	67/67/29	672.9 (21.6)	651.1 (21.7)	647.1 (33.2)	.339	2, 159	.71	.86	.89	1.00	.12	.14	.02
Stop-signal reaction time, SSRT (ms)	65/65/27	298.1 (7.8)	277.1 (7.8)	292.9 (12.1)	1.885	2, 153	.16	.17	.98	.62	.33	.08	.25

Means and standard errors. ANCOVA (all groups, corrected for age). Significant p values are shown in bold.
The robustness of these parametric tests was confirmed using bootstrap simulations with 1000 replications. Thereby, no pairwise Sidak post-hoc comparison above turned from a significant group difference into a non-significant.
[a] Sample size control group/RCU/DCU. For details see *Statistical analysis*.
[b] p( ) = Percentage.
[c] RT = Reaction time.

Table 4
Correlations between cocaine use parameters, ADHD, BDI, and measures of impulsivity in cocaine users

	BIS-11				TCI NS					RVP				SST						
	FI	FII	FIII	Total score	NS1	NS2	NS3	NS4	Total score	B"	M. Lat.	Total FA	Imp.-score	p[c] (corr. inhib)	RT[d] go trials	p[c] (corr. resp)	RT[d] s-r trials	SSRT	ADHD[e]	Depr.[f]
Times per week[a]	.19				-.18			-.19	-.19											
Grams per week log[a]					-.05			*-.21												
Years of use[a]	*.24	*.24	*.25	**.29															*.21	.19
Years of use, adj. for age[b]	**.30	**.30	**.33	***.37		.17													*.24	*.22
Age of onset[a]	-.18	-.19	*-.22	*-.24													.19			
Cumulative dose (grams) log[a]	**.27	**.28	*.23	**.31	-.18		.20												**.28	***.33
Cumulative dose (grams) log, adj. for age[b]	**.28	**.30	*.25	***.33	-.19														**.29	***.35
Maximum dose (grams/day)[a]					-.18														**.26	**.27
CCQ sum score (0-70)[a]	***.33			*.22	-.19							.19					*-.22		**.29	***.33
Hair analysis $Cocaine_{total}$ pg/mg[a]					*-.25															
Hair analysis Cocaine pg/mg[a]					*-.23															
Hair analysis Benzoylecgonine pg/mg[a]					**-.32													.19		
Hair analysis Cocaethylene pg/mg[a]																				
Hair analysis Norcocaine pg/mg[a]					*-.26*				-.18											

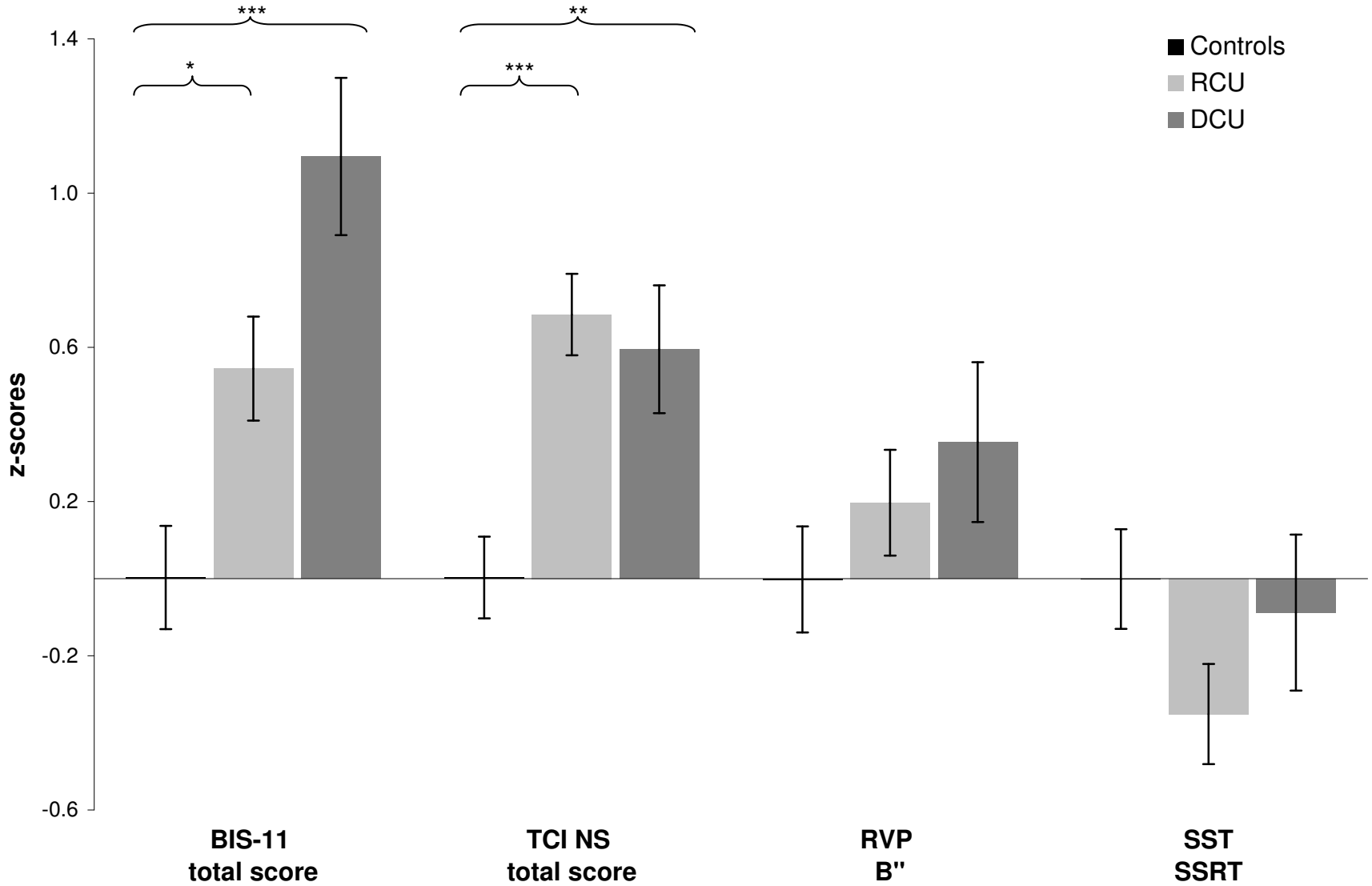
Correlations with a p-level below 10% are shown, while significant correlations are marked: *p<.05; **p<.01; ***p<.001.
[a] Pearson's product-moment correlation.
[b] Partial Correlation corrected for age.
[c] p( ) = Percentage.
[d] RT = Reaction time.
[e] ADHD as measured by number of ADHD symptoms in ADHD-SR.
[f] Depression as measured by BDI score.

Table 5
Correlation matrix for impulsivity measures, ADHD, and BDI in cocaine users

	2)	3)	4)	5)	6)	7)	8)	9)	10)	11)	12)	13)	14)	15)	16)	17)	18)	19)	20)
1) BIS-11 FI Attentional Imp.	***.51	***.43	***.75		**.23	.14	**.24	*.19										***.75	***.50
2) BIS-11 FII Motor Imp.	1	***.66	***.88		***.50	***.32	***.37	***.49	*-.20		*.18	*.16	-.13					***.47	***.31
3) BIS-11 FIII Nonplanning Imp.		1	***.85		***.51	***.40	***.41	***.47					**-.21	*-.19		*-.16		***.36	***.27
4) BIS-11 Total score			1		***.51	***.35	***.41	***.47	-.15		.13		*-.18	-.13				***.61	***.42
5) TCI NS1 Exploratory excitability				1	**.21	*.16	.13	***.57									*-.16		***-.37
6) TCI NS2 Impulsiveness					1	***.34	***.35	***.74	-.15		.14	*.19						*.16	
7) TCI NS3 Extravagance						1	***.42	***.70										.13	
8) TCI NS4 Disorderliness							1	***.69						**-.22		*-.18		***.28	
9) TCI Novelty seeking Total score								1				*.16		-.15				*.17	
10) RVP Response bias B"									1	**-.23	***-.96	***-.69					.14		
11) RVP Mean latency										1	***.27	***-.51							
12) RVP Total false alarms											1	***.69							
13) RVP Impulsivity-score												1							
14) SST p(correct inhibition)[c]													1	***.63	***-.32	***.56	***-.40		
15) SST RT on go trials[d]														1	***-.51	***.95	**-.25		
16) SST p(correct resp. on go trials)[c]															1	***-.54	***.52		
17) SST RT on signal-respond trials[d]																1	***-.32		
18) SST Stop-signal reaction time																	1		
19) ADHD[a]																		1	***.56
20) Depression[b]																			1

Pearson's product-moment correlation. Correlations with a p-level below 10% are shown, while significant correlations are marked: *p<.05; **p<.01; ***p<.001.
[a] ADHD as measured by number of ADHD symptoms in ADHD-SR.
[b] Depression as measured by BDI score.
[c] p( ) = Percentage.
[d] RT = Reaction time.

Figure 1


***
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*
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1.4
1.0
0.6
0.2
-0.2
-0.6
z-scores
Controls
RCU
DCU
BIS-11
total score
TCI NS
total score
RVP
B"
SST
SSRT

Supplementary material

Differences in self-reported and behavioral measures of impulsivity in recreational and dependent cocaine users

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Supplementary Methods1: Recruitment and selection

The recruitment focused on the greater area of Zurich and lasted from January 2010 until January 2012. Participants were recruited via advertisements in local newspapers, online media, drug prevention and treatment centers, psychiatric hospitals, and by word of mouth. Eight-hundred-four prospective participants underwent a standardized telephone interview, whereof 240 subjects were considered to be eligible for the study at the University Hospital of Psychiatry in Zurich. All subjects were considered eligible to the study if they had sufficient German language skills and were aged between 18 and 60 years Forty-six participants had to be excluded afterwards due to hair analyses revealing illegal drug use not declared in the interviews (e.g., opioids, excessive MDMA use), a polytoxic drug use pattern, or lack of cocaine use. Furthermore, the data of four participants (3 controls, 1 cocaine user) could not be analyzed because of technical problems during the test session and 24 participants were excluded due to matching reasons (age, verbal IQ, and smoking) between groups (15 controls, 9 cocaine users). Hair samples were provided by 163 subjects, as hair analysis was not possible due to an insufficient amount of hair for two controls and one cocaine user.

Supplementary Methods 2: Urine and hair toxicologies

Urine toxicology analyses comprised the compounds/substances: tetrahydrocannabinol, cocaine, amphetamines, benzodiazepines, opioids, and methadone and were assessed by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany).

To characterize drug use over the last six months objectively, hair samples were collected and analyzed with Liquid chromatography-tandem mass spectrometry (LC-MS/MS). If participants' hair was long enough, one sample of six cm hair (from the scalp) was taken and subsequently divided into two subsamples of three cm length. The following compounds were assessed: cocaine, benzoylecgonine, ethylcocaine, norcocaine, amphetamine, methamphetamine, MDMA, MDEA, MDA, morphine, codeine, methadone EDDP (primary methadone metabolite), tramadol, and methylphenidate.

For our routine protocol for drugs of abuse analysis a three step washing procedure with water (2 minutes shaking, 15ml), acetone (2min., 10ml) and finally hexane (2min., 10ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5ml, 16hours, ultrasonication) and a second step with 3 ml MeOH acidified with 50 µL

hydrochloric acid 33 % (3 hours, ultrasonication). The extracts were dried and the residue reconstituted with 50 µL MeOH and 500 µL 0.2 mM ammonium formate (analytical grade) in water. As internal standards deuterated standards of the following compounds were used, added as mixture of the following compounds: cocaine-d3, benzoylecgonine-d3, ethylcocaine-d3, morphine-d3, MAM-d3, codeine-d3, dihydrocodeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5. MDEA-d6, MDA-d5, methadone-d9, EDDP-d3, methylphenidate-d9, tramadol-d3, oxycodone-d3, and ephedrine-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and obtained from Merck (Darmstadt, Germany); LC-solvents were of HPLC grade and were obtained from Sigma Aldrich (Buchs, Switzerland).

The LC-MS/MS apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20 psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven, Shimadzu, Duisburg, Germany). Gradient elution was performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex, Aschaffenburg, Germany). The mobile phase consisted of 1mM ammonium formate buffer adjusted to pH 3,5 with formic acid (eluent A) and acetonitrile containing 1mM ammonium formate and 1 mM formic acid (eluent B). The Analysis was performed in MRM mode with two transitions per analyte and one transition for each deuterated internal standard, respectively.

Supplementary Methods 3: Impulsivity assessment

The *Barratt Impulsiveness Scale (BIS-11)* (Patton et al., 1995) is a commonly administered (Stanford et al., 2009), internally consistent (Patton et al., 1995), and well validated self-report measure for the assessment of trait impulsivity in both research and clinical settings (Reynolds et al., 2006). It consists of 30 items which, based on principal component analysis, can be reduced to three subscores labeled *attentional*, *motor*, and *non-planning* impulsivity and a *total score* (Patton et al., 1995).

The 240-item *Temperament and Character Inventory (TCI)* (Cloninger et al., 1999; Cloninger et al., 1993) is a questionnaire to assess basic personality dimensions of temperament and character. In this paper, we only analyzed the temperament factor novelty seeking (NS) because it is closely related to common impulsivity constructs. *The novelty seeking total score* describes a heritable pattern of behavior that comprises exploration in response to novelty and cues of reward, impulsive decision making, and quick loss of temper (Cloninger et al., 1993). It consists of 40 items that can be subdivided into four subscales (*exploratory excitability vs. stoic rigidity*, *impulsiveness vs. reflection*, *extravagance vs. reserve*, *disorderliness vs. regimentation*).

The *Rapid Visual Processing Task (RVP)* is a test of sustained attention from the Cambridge Neuropsychological Test Automated Battery (CANTAB; www.cantab.com) that has previously proved useful in several studies investigating cocaine use (Ersche et al., 2011; Soar et al., 2012; Vonmoos et al., in press). As attention is a cognitive component closely related to impulsive behavior and substance use (de Wit, 2009; Evenden, 1999; Garavan and Hester, 2007), and attentional impairments have previously been reported in recreational (Soar et al., 2012; Vonmoos et al., in press) as well as chronic cocaine users (Ersche et al., 2011; Jovanovski et al., 2005), we applied some impulsivity-related RVP parameters in order to increase the number impulsive behavior measures. In this regard, especially the *response bias B''* (response bias) reflects the tendency to respond regardless of the presence of a target and can therefore be interpreted as a measure for impulsive behavior (Nuechterlein, 1983). Additionally, impulsive behavior can be reflected by an increased number of *false alarms* paired with short response *latencies* (Ersche et al., 2011). Therefore, we analyzed these parameters separately and in combination, as we applied an *Impulsivity-score*, a composite index that reflects impulsivity on the dimension fast-inaccurate to slow-accurate and is calculated by subtracting standardized mean latency scores from errors scores (I-score=$z_{\text{false alarms}} - z_{\text{latency}}$)(Salkind and Wright, 1977). Both values were z-transformed on the basis of means and standard deviations of the control group.

The *stop-signal reaction task (SST)* (Logan, 1994; Verbruggen et al., 2008) is an operational measure for inhibitory motor control (Perry and Carroll, 2008) and has been widely used to study behavioral impulsivity in cocaine users (Ersche et al., 2012; Fillmore and Rush, 2002; Hester and Garavan, 2004). The task requires subjects to respond quickly to pseudo-randomly presented visual go-signals on a computer screen (arrows to left and right with a probability of 50% each) and to inhibit a response shortly after the

presentation of an auditory stop-signal (in 25% of all trials). First, we conducted a practice phase with 32 trials (not analyzed) and then 3 blocks of 64 trials (for further details to this task see Verbruggen et al. (2008). A staircase tracking procedure systematically varied the time between the go- and stop-signals until the stop-signal delay (SSD) was found at which the participant was able to inhibit the response on approximately 50%. The *stop signal reaction time (SSRT)* provided an estimation for response inhibition, a fundamental feature of impulsive motor behavior (de Wit, 2009). Additionally, we analyzed further stop-signal variables as recommended by Verbruggen et al. (2008): *percentage of correct inhibition*, *reaction time on go trials, percentage of correct responses on go trial*s, and *reaction time on signal-respond trials*.

Supplementary Methods 4: Group assignment for cofactors

Possible confounding factors of impulsivity were defined based on theoretical a priori considerations (Chaves et al., 2011; Perez de Los Cobos et al., 2011; Swendsen and Merikangas, 2000; Tziortzis et al., 2011; Vonmoos et al., in press; Wilson, 2007). To test the supposed relations of specific confounding factors with impulsivity, a consolidated CU group was divided according to cofactor criteria and the two resulting CU subgroups were compared with the controls.

To test the influence of *recent cocaine use*, cocaine users were divided into users with positive (range: 217-24'888 ng/ml, mean: 3'873 ng/ml, SD: 6'461 ng/ml) and negative urine samples (Supplementary Table 3). Analogously, the influence of *recent cannabis use* was investigated by dividing cocaine users into users with positive (range: 60–726 ng/ml, mean: 125 ng/ml, SD: 143 ng/ml) and users with negative urine samples for THC. They were compared with controls featuring negative urine samples, as we excluded 10 controls displaying positive cannabis urine samples. *Age of onset* subgroups were divided according to a cut-off value of 18 years and *duration of cocaine use* subgroups were splitted according to a cut-off value of 10 years, separating the quarter of cocaine users in our sample, which had the longest duration of cocaine use. As *cocaine binge* is defined as out-of-control intake of large amounts of cocaine over an extended period of time (Mutschler et al., 2001), high *cocaine binge* was defined as an average cocaine use of at least 2g per occasion during the last 6 months. Cocaine user subgroups for *ADHD* (with/without ADHD,) and *depression* (no/at least mild, BDI $\geq$11, excluding 5 controls with BDI $\geq$11) were created according to predefined diagnostic criteria (Hautzinger et al., 1994; Roesler et al., 2004), for *craving* by median split (low/high, CCQ $\leq$16).

Supplementary Table 1: Impulsivity measures (ANOVA, without correction for age)

Measure	n[a]	Controls	RCU	DCU	F	df, df_{err}	p	p, Sidak post-hoc			Cohen's d		
								Controls vs. RCU	Controls vs. DCU	RCU vs. DCU	Controls vs. RCU	Controls vs. DCU	RCU vs. DCU
Barratt Impulsiveness Scale (BIS-11)													
FI Attentional Impulsiveness	68/68/30	14.7 (3.1)	16.4 (3.9)	18.6 (4.1)	12.551	2, 163	**<.001**	**.02**	**<.001**	**.02**	.44	1.01	.58
FII Motor Impulsiveness	68/68/30	22.5 (3.9)	24.4 (4.5)	25.8 (5.8)	6.271	2, 163	**.002**	**.05**	**.003**	.42	.41	.70	.30
FIII Nonplanning Impulsivenes	68/68/30	26.3 (4.7)	27.9 (4.1)	28.9 (4.9)	4.438	2, 163	**.01**	.09	**.02**	.68	.37	.58	.22
BIS-11 Total score	68/68/30	63.4 (9.4)	68.7 (10.2)	73.3 (12.7)	10.425	2, 163	**<.001**	**.01**	**<.001**	.13	.48	.90	.42
Temperament and Character Inventory													
NS1 Exploratory excitability	67/68/28	7.4 (2.1)	8.1 (2.1)	7.1 (2.6)	2.319	2, 160	.10	.29	.87	.16	.28	.15	.43
NS2 Impulsiveness	67/68/28	4.8 (2.5)	5.9 (2.4)	5.9 (2.3)	4.313	2, 160	**.01**	**.02**	.16	1.00	.47	.42	.05
NS3 Extravagance	67/68/28	5.8 (2.3)	7.1 (1.7)	7.4 (1.8)	9.559	2, 160	**<.001**	**<.001**	**.001**	.85	.61	.76	.16
NS4 Disorderliness	67/68/28	4.4 (1.9)	5.8 (1.9)	5.5 (1.9)	10.465	2, 160	**<.001**	**<.001**	**.02**	.84	.73	.57	.16
Novelty seeking Total score	67/68/28	22.5 (6.3)	27.0 (4.9)	25.9 (4.8)	11.648	2, 160	**<.001**	**<.001**	**.02**	.78	.76	.58	.18
Rapid Visual Processing Task													
Response bias B"	67/68/30	.948 (0.1)	.938 (0.1)	.925 (0.1)	1.302	2, 162	.27	.74	.31	.77	.16	.35	.19
Mean latency (ms)	67/68/30	404.7 (86.2)	417.8 (92.3)	417.2 (91.9)	.412	2, 162	.66	.78	.89	1.00	.15	.14	.01
Total false alarms	67/68/30	1.3 (1.6)	1.9 (1.9)	2.2 (2.7)	2.951	2, 162	.06	.22	.08	.78	.30	.48	.19
Impulsivity-score	67/68/30	.00 (1.2)	.22 (1.3)	.46 (1.9)	1.189	2, 162	.31	.74	.35	.82	.16	.33	.17
Stop-Signal Task													
p(correct inhibition)	67/67/29	54.8 (9.1)	54.5 (11.0)	50.9 (15.1)	1.337	2, 160	.27	1.00	.32	.39	.03	.35	.32
RT on go trials (ms)	67/67/29	765.8 (187)	723.2 (199)	746.0 (188)	.819	2, 160	.44	.49	.96	.93	.22	.10	.12
p(correct responses on go trials)	67/67/29	94.4 (9.8)	91.9 (12.7)	93.6 (10.2)	1.501	2, 160	.23	.26	.99	.67	.29	.06	.23
RT on signal-respond trials (ms)	67/67/29	673.5 (177)	644.8 (191)	660.2 (163)	.421	2, 160	.66	.74	.98	.97	.16	.07	.09
Stop-signal reaction time, SSRT (ms)	65/65/27	298.2 (60.1)	276.8 (59.7)	293.5 (73.4)	2.021	2, 154	.14	.15	.98	.56	.34	.07	.27

Means and standard deviations. ANOVA (all groups). Significant p values are shown in bold.
[a] Sample size control group/RCU/DCU. For details see the methods part *Statistical analysis*.

Supplementary Table 2: Intercorrelation of cocaine use parameters in cocaine users

	2)	3)	4)	5)	6)	7)	8)	9)	10)	11)	12)
1) Cumulative dose (grams) log	*.24	*.22	***.57	.02	***.62	-.09	***.34	***.37	*.21*	***.39	***.36
2) Times per week	1	***.70	-.09	.09	.17	.15	.18	.14	*.23	.16	.18
3) Grams per week log		1	-.13	.04	.13	.13	.04	-.04	.18	-.01	.03
4) Years of use			1	-.03	.06	-.10	***.42	***.37	***.37	***.39	***.42
5) Age of onset				1	.07	-.17	.16	.20	.05	.17	.17
6) Maximum dose (grams/day)					1	-.09	.14	*.23	-.08	*.22	.16
7) CCQ sum score (0-70)						1	.03	-.01	-.03	.01	.02
8) Hair analysis Cocaine pg/mg							1	***.91	***.70	***.86	***1.00
9) Hair analysis Benzoylecgonine pg/mg								1	***.55	***.95	***.94
10) Hair analysis Cocaethylene pg/mg									1	***.62	***.68
11) Hair analysis Norcocaine pg/mg										1	***.89
12) Hair analysis $Cocaine_{total}$ pg/mg											1

Analyses only for cocaine users (n=98; Hair samples were voluntary and are deficient for 1 RCU).
Pearson's product-moment correlation. Significant correlations (two-tailed) are marked: *p<.05; **p<.01; ***p<.001.

Supplementary Table 3: Cofactor analyses

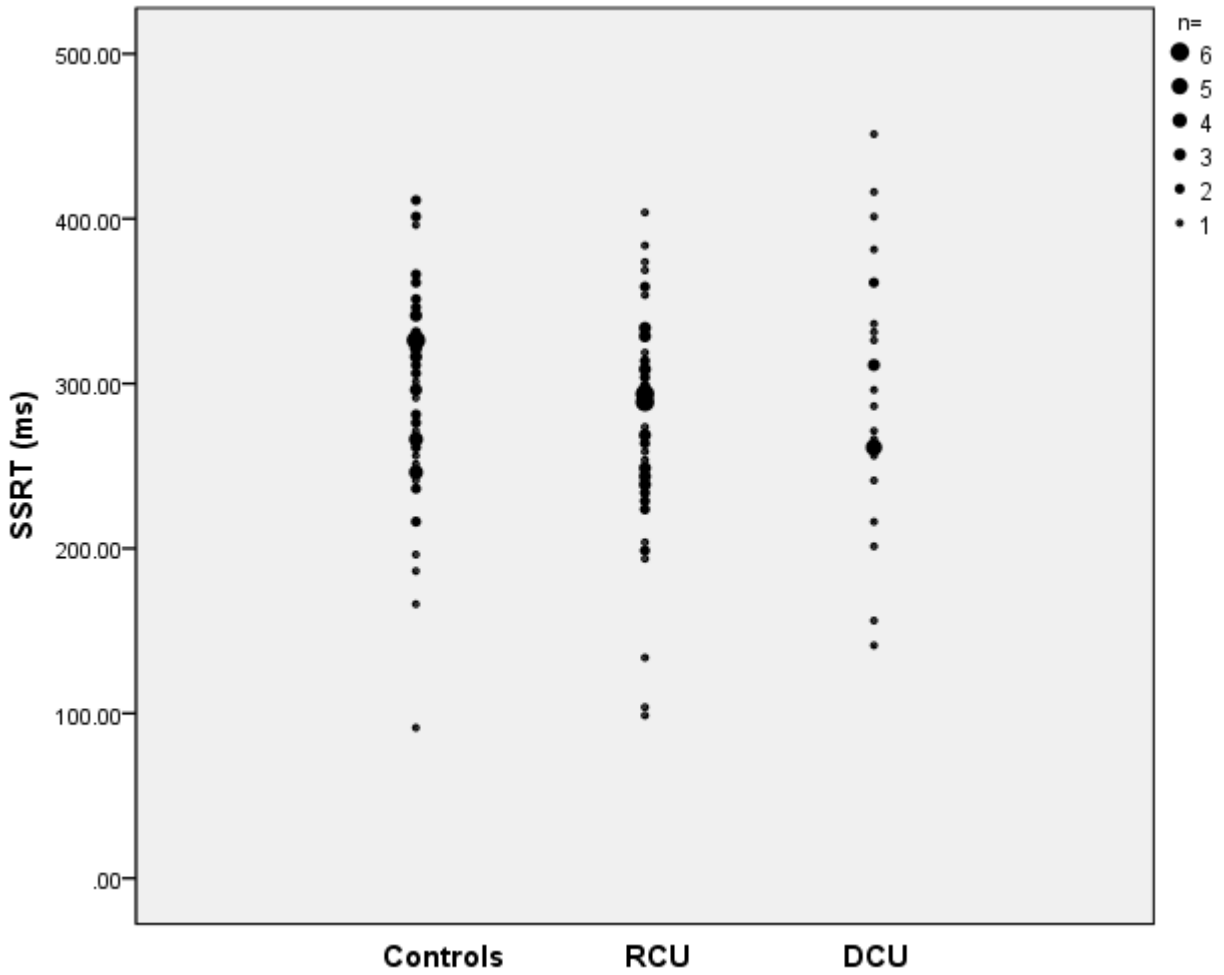
	n	Controls	CU 1	CU 2	F	df, df_{err}	p	p, Sidak post-hoc: Controls vs CU 1	p, Sidak post-hoc: Controls vs CU 2	p, Sidak post-hoc: CU 1 vs CU 2	Cohen's d: Controls vs CU 1	Cohen's d: Controls vs CU 2	Cohen's d: CU 1 vs CU 2
Urine toxicology Cocaine			*UP-*	*UP+*									
BIS-11 total	68/75/22	63.4 (1.3)	70.2 (1.2)	69.2 (2.2)	7.854	2, 161	**<.001**	**<.001**	.08	.97	.62	.53	.09
TCI NS	67/74/21	22.5 (0.7)	26.8 (0.6)	26.2 (1.2)	11.221	2, 158	**<.001**	**<.001**	**.02**	.97	.72	.63	.09
RVP B"	67/75/22	0.949 (0.0)	0.940 (0.0)	0.915 (0.0)	2.125	2, 160	.12	.80	.12	.34	.14	.51	.38
SSRT	65/71/21	298.1 (7.8)	283.5 (7.4)	276.1 (13.7)	1.397	2, 153	.25	.44	.42	.95	.23	.35	.12
Urine toxicology Cannabis			*UP-*	*UP+*									
BIS-11 total	58/75/22	62.8 (1.4)	69.4 (1.2)	72 (2.2)	6.048	3, 160	**<.001**	**.003**	**.003**	.88	.60	.84	.24
TCI NS	57/73/22	22.3 (0.7)	26.7 (0.6)	26.6 (1.2)	7.538	3, 157	**<.001**	**<.001**	**.01**	1.00	.74	.72	.02
RVP B"	57/75/22	0.948 (0.0)	0.936 (0.0)	0.928 (0.0)	.729	3, 159	.54	.89	.79	1.00	.18	.30	.12
SSRT	57/71/21	300.6 (8.4)	282.8 (7.5)	278.1 (13.7)	1.124	3, 152	.34	.52	.65	1.00	.28	.36	.08
Age of onset			*Onset >18*	*Onset ≤18*									
BIS-11 total	68/25/73	63.4 (1.3)	68.6 (1.2)	74.5 (2.2)	11.087	2, 162	**<.001**	**<.001**	**.01**	.06	1.02	.47	.55
TCI NS	67/24/72	22.5 (0.7)	26.5 (0.7)	27.2 (1.2)	11.451	2, 159	**<.001**	**.002**	**<.001**	.92	.80	.67	.13
RVP B"	67/25/73	0.949 (0.0)	0.94 (0.0)	0.916 (0.0)	2.054	2, 161	.13	.13	.83	.37	.50	.14	.36
SSRT	65/22/70	298.1 (7.8)	280.3 (7.6)	286.7 (14.0)	1.363	2, 153	.26	.86	.28	.97	.18	.28	.10
Duration of cocaine use			*≤10 years*	*>10 years*									
BIS-11 total	68/75/23	63.5 (1.2)	67.8 (1.2)	77.3 (2.3)	15.091	2, 162	**<.001**	**.04**	**<.001**	**.001**	.40	1.27	.87
TCI NS	67/73/23	22.5 (0.7)	26.1 (0.7)	28.5 (1.2)	12.861	2, 159	**<.001**	**<.001**	**<.001**	.26	.61	1.01	.41
RVP B"	67/75/23	0.949 (0.0)	0.928 (0.0)	0.953 (0.0)	1.998	2, 161	.14	.20	.99	.40	.31	.07	.37
SSRT	65/71/21	298.0 (7.8)	284.9 (7.6)	271.3 (14.7)	1.609	2, 153	.20	.55	.29	.81	.21	.43	.22
Binge			*low*	*high*									
BIS-11 total	68/74/24	63.4 (1.3)	69.8 (1.2)	70.8 (2.1)	8.131	2, 162	**<.001**	**.001**	**.01**	.97	.59	.67	.09
TCI NS	67/73/23	22.5 (0.7)	26.4 (0.6)	27.4 (1.1)	11.595	2, 159	**<.001**	**<.001**	**<.001**	.83	.66	.83	.17
RVP B"	67/74/24	0.949 (0.0)	0.940 (0.0)	0.915 (0.0)	2.389	2, 161	.09	.84	.09	.26	.12	.51	.39
SSRT	65/69/23	298.1 (7.8)	284.7 (7.5)	273.2 (13.1)	1.579	2, 153	.21	.52	.28	.83	.21	.40	.18

Supplementary Table 3: Cofactor analyses (cont.)

	n	Controls	CU 1	CU 2	F	df, df_{err}	p	p, Sidak post-hoc			Cohen's d		
								Controls vs CU 1	Controls vs CU 2	CU 1 vs CU 2	Controls vs CU 1	Controls vs CU 2	CU 1 vs CU 2
Craving			*low*	*high*									
BIS-11 total	68/52/46	63.4 (1.3)	68.8 (1.5)	71.5 (1.5)	8.911	2, 162	**<.001**	**.02**	**<.001**	.51	.49	.74	.24
TCI NS	67/51/45	22.5 (0.7)	27.3 (0.8)	25.9 (0.8)	12.180	2, 159	**<.001**	**<.001**	**.005**	.50	.82	.58	.24
RVP B"	67/52/46	0.949 (0.0)	0.941 (0.0)	0.927 (0.0)	1.509	2, 161	.224	.88	.23	.66	.12	.33	.21
SSRT	65/47/45	298.1 (7.8)	279.4 (9.2)	284.3 (9.4)	1.355	2, 153	.261	.32	.59	.98	.30	.22	.08
ADHD diagnosis			*w/out ADHD*	*with ADHD*									
BIS-11 total	68/76/22	63.4 (1.2)	67.2 (1.1)	80.0 (2.1)	24.384	2, 162	**<.001**	.06	**<.001**	**<.001**	.35	1.51	1.17
TCI NS	67/75/21	22.5 (0.7)	26.2 (0.6)	28.3 (1.2)	12.618	2, 159	**<.001**	**<.001**	**<.001**	.33	.63	.98	.35
RVP B"	67/76/22	0.949 (0.0)	0.936 (0.0)	0.928 (0.0)	1.071	2, 161	.34	.57	.51	.95	.20	.32	.12
SSRT	65/72/20	298.1 (7.8)	278.5 (7.4)	293.6 (14.0)	1.745	2, 153	.18	.19	.99	.72	.31	.07	.24
Depressive symptoms			*low*	*≥mild*									
BIS-11 total	63/69/29	63.7 (1.3)	67.7 (1.2)	75.8 (1.9)	13.997	2, 157	**<.001**	.08	**<.001**	**.001**	.36	1.10	.74
TCI NS	62/67/29	23.0 (0.7)	27.4 (0.7)	25.0 (1)	10.940	2, 154	**<.001**	**<.001**	.29	.12	.77	.34	.43
RVP B"	62/69/29	0.951 (0.0)	0.932 (0.0)	0.939 (0.0)	1.310	2, 156	.27	.29	.84	.94	.29	.18	.11
SSRT	60/65/27	297.4 (8.1)	275.9 (7.8)	295.9 (12.1)	2.071	2, 148	.13	.17	1.00	.43	.34	.02	.31

Means and standard errors. ANCOVA (all groups, corrected for age). Significant p values are shown in bold.
[a] Sample size control group/CU 1/CU 2. For details see the methods part *Statistical analysis*.

Supplementary Figure 1: SSRT analysis



Separated for control group (n=65), recreational cocaine user group (n=65), and dependent cocaine user group (n=27).

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